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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/579,606	05/16/2006	Susanne Moira Brown	6947-75756-01	9388

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EXAMINER
KINSEY WHITE, NICOLE

ART UNIT	PAPER NUMBER
1648	

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10/31/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/579,606	BROWN ET AL.	
	Examiner	Art Unit	
	Nicole E. Kinsey, Ph.D.	1648	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *02 August 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-4,7-26,31-34,36,37,42,51 and 53-64* is/are pending in the application.

4a) Of the above claim(s) *31,51,53-56,58 and 59* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,4,7-26,32-34,36,37,42,57 and 60-64* is/are rejected.

7)☒ Claim(s) *3* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☒ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *7/13/2006*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Applicants' election without traverse of Group I (claims 1-4, 7-26, 32-34, 36-37, 42, 57 and 60-64) in the reply filed on August 2, 2007 is acknowledged.

Oath/Declaration

The oath or declaration is defective. A new oath or declaration in compliance with 37 CFR 1.67(a) identifying this application by application number and filing date is required. See MPEP §§ 602.01 and 602.02.

The oath or declaration is defective because the declaration for Paul Dunn does not refer to the specification or prior applications to which the oath or declaration is directed. See MPEP § 602.

Specification

The title of the invention is not descriptive. A new title is required that is clearly indicative of the invention to which the claims are directed. Appropriate correction is required.

Claim Objections

Claims 3 and 4 are objected to because of the following informalities: Claims 3 and 4 should recite SEQ ID NO:X instead of SEQ ID No.X. Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim 4 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim contains subject matter, which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention.

The claim is drawn to, *inter alia*, a herpes simplex virus comprising a nucleic acid having (a) at least 60% sequence identity to SEQ ID NO:2 or to a nucleic acid encoding the polypeptide of SEQ ID NO:1; (b) at least 70% sequence identity to SEQ ID NO:2 or to a nucleic acid encoding the polypeptide of SEQ ID NO:1; or (c) that hybridizes to the nucleic acid of SEQ ID NO:2, to its complement or to a nucleic acid encoding the polypeptide of SEQ ID NO:1 under high stringency conditions.

The written description rejection is made because the claims are interpreted as being drawn to a genus of polypeptides recited as having at least 60% identity with SEQ ID NO:2 or to a nucleic acid encoding the polypeptide of SEQ ID NO:1. The applicable standard for the written description requirement can be found in MPEP 2163; University of California v. Eli Lilly, 43 USPQ2d 1398 at 1407; PTO Written Description Guidelines; Enzo Biochem Inc. v. Gen-Probe Inc., 63 USPQ2d 1609; Vas- Cath Inc. v. Mahurkar, 19 USPQ2d 1111; and University of Rochester v. G.D. Searle & Co., 69 USPQ2d 1886

(CAFC 2004). To provide adequate written description and evidence of possession of a claimed genus, the specification must provide sufficient distinguishing identifying characteristics of the genus. The factors to be considered include disclosure of complete or partial structure, physical and/or chemical properties, functional characteristics, structure/function correlation, methods of making the claimed product, or any combination thereof. In this case, the only factor present in the claims is SEQ ID NO:2 (and SEQ ID NO:1) and the function of SEQ ID NO:2 (i.e., nitroreductase activity). There is no disclosure of any particular portion of the structure that must be conserved or that can be altered in order to be at least 60% identical with SEQ ID NO:2 and retain the indicated function.

The specification discloses at pages 6 and 7 that "[a]lternatively the nucleic acid may have at least 60% sequence identity to SEQ ID No. 2. Said degree of sequence identity may alternatively be one of at least 70%, 80%, 90%, 95%, 96%, 97%, 98% or 99% provided the polypeptide or protein encoded by such nucleic acid has a nitroreductase function." However, the specification does not indicate which portions of SEQ ID NO:2 are essential to retain the nitroreductase function or which portions of SEQ ID NO:2 can be modified or altered and still retain the nitroreductase function.

Accordingly, in the absence of sufficient recitation of distinguishing identifying characteristics, the specification does not provide adequate written description of the claimed genus. A definition by function alone does not suffice to sufficiently describe a coding sequence because it is only an indication of what the gene does, rather than what it is. EliLily, 119 F.3 at 1568, 43 USPQ2d at 1406.

The court clearly states in Vas-Cath Inc. v. Mahurkar, 19 USPQ2d 1111, that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the 'written description' inquiry, whatever is now claimed." (See page 1117.) The specification does not clearly allow persons of ordinary skill in the art to recognize that the inventors invented what is claimed. As discussed above, the skilled artisan cannot envision the detailed chemical structure of the encompassed genus of proteins that are have at least 60% identity with SEQ ID NO:2. Given that the specification has only described the structure of SEQ ID NO:2 and the function of the encoded protein, the full breadth of the claims does not meet the written description provision of 35 U.S.C. 112, first paragraph.

Claim 57 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter, which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Where an invention is, or relies on, a biological material, the disclosure may include reference to a deposit of such biological material. Applicants claim HSV strain HSV1716/CMV-NTR/GFP. As such, the strain must be readily available or obtainable by a repeatable method set forth in the specification, or otherwise readily available to the public. If it is not so obtainable or available, the requirements of 35 USC 112, first paragraph, may be satisfied by a deposit of the strain.

The claimed HSV strain (HSV1716/CMV-NTR/GFP) disclosed in the specification does not appear to be produced from a repeatable process, and it is not apparent if HSV1716/CMV-NTR/GFP is both known and readily available to the public. It is noted that page 6 of the specification and claim 57 indicate that the HSV strain has been deposited; however, there is no indication in the specification as to public availability.

If the deposit was made under the terms of the Budapest Treaty, then a statement, affidavit or declaration by applicants, or a statement by an attorney of record over his or her signature and registration number, or someone empowered to make such a statement, stating that the instant invention will be irrevocably and without restriction released to the public upon the issuance of a patent, would satisfy the deposit requirement.

If the deposit was not made under the Budapest Treaty, then in order to certify that the deposit meets the criteria set forth in 37 CRF 1.801-1.809 and MPEP 2402-2411.05, applicants may provide assurance of compliance by statement, affidavit or declaration or by someone empowered to make the same or by a statement by an attorney of record over his or her signature and registration number showing that:

(a) during the pendency of the application, access to the invention will be afforded to the Commissioner upon request;

(b) all restrictions upon availability to the public will be irrevocably removed upon granting of the patent;

(c) the deposit will be maintained in a public depository for a period of 30 years or 5 years after the last request or for the enforceable life of the patent, whichever is longer;

(d) a test of the viability of the biological material at the time of deposit (see 37 CFR 1.807); and

(e) the deposit will be replaced if it should ever become inviable.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

Claim 4 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 4 recites "high stringency conditions." The specification at pages 29-32 provides a definition of hybridization stringency and provides general hybridization conditions. However, neither the claim nor the specification provides specific parameters for "high stringency conditions," i.e., temperature, salt concentration, wash conditions, etc. One would not know what range of conditions is encompassed by the phrase "high stringency conditions." Therefore, one cannot determine the metes and bounds of the claim.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1, 2, 4, 7-16, 32-34, 60 and 61 are rejected under 35 U.S.C. 102(b) as being anticipated by Coffin et al. (WO 99/38955) as evidenced by Anlezark et al. (WO 93/08288).

The claims are drawn to, *inter alia*, a herpes simplex virus wherein the herpes simplex virus genome comprises nucleic acid encoding an heterologous nitroreductase (NTR).

Coffin et al. discloses herpes viral genomes comprising a heterologous gene, which can be "bacterial nitroreductase such as E. coli nitroreductase as disclosed in WO 93/108288." (see pages 6-9, especially page 9, lines 15-23). The nitroreductase of WO 93/108288 (Anlezark et al.) is 97% identical to instant SEQ ID NO:2 (see attached alignment).

The constructs of Coffin et al. further comprise a regulatory sequence (i.e., promoter) operably linked to the nucleic acid encoding the NTR (see page 6, line 28 to page 7, line 10). The ICP34.5 gene of HSV can be rendered functionally inactive by deletions, substitutions or by inserting the heterologous gene within the ICP34.5 sequence (see page 5, lines 15-29, especially 24-25). Coffin et al. teaches the use of HSV strain 17+ (see page 12). One or both copies of ICP34.5 can be deleted (see page 2, lines 29-34; page 3, lines 6-11; and page 12, lines 5-17). Further, the HSV can be non-neurovirulent (see page 2, lines 3-13 and page 14 line 29 to page 15, line 2).

Furthermore, the constructs of Coffin et al. can be formulated as a vaccine or pharmaceutical composition (see page 9, lines 24-26 and page 10, lines 15-21).

Therefore, Coffin et al. anticipates the claimed invention.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 17-26 are rejected under 35 U.S.C. 103(a) as being unpatentable over Coffin et al. as applied to claims 1, 2, 4, 7-16, 32-34, 60 and 61 above, and further in view of Herlitschka et al. (U.S. Patent No. 6,114,146).

The claims are drawn to a herpes simplex virus comprising a nucleic acid cassette integrated in the genome of said herpes simplex virus, said cassette encoding:

(a) said nucleic acid encoding NTR;

(b) nucleic acid encoding a ribosome binding site; and

(c) a marker,

wherein the nucleic acid encoding NTR is arranged upstream (5') of the ribosome binding site and the ribosome binding site is arranged upstream (5') of the marker.

In addition to the teachings of Coffin et al. outlined above, Coffin et al. also teaches an expression cassette comprising one or more heterologous genes, where one gene can be NTR and the other gene can be a marker such as GFP and each gene can have its own promoter (see page 9, lines 15-30). The constructs of Coffin et al. can optionally include the associated transcriptional control sequences normally associated with the transcribed sequences, for example transcriptional stop signals, polyadenylation sites and downstream enhancer elements (see page 6, lines18-20).

Coffin et al. does not teach use of a ribosome binding site, the arrangement of the cassette and use of the SV40 polyadenylation signal. However, Herlitschka et al. discloses a dicistronic expression cassette comprising a foreign gene, a fusion gene comprising a marker and a ribosome binding site located between the foreign gene and the marker gene. According to a preferred embodiment, the encoding sequence for the foreign protein lies 5' and the encoding sequence for the fusion protein lies 3' from the internal ribosome binding site. This arrangement enables a maximum yield of foreign protein, since the gene for the foreign protein is located immediately downstream of the promoter and thus is optimally transcribed (see col. 5, lines 48-65). Further, Herlitschka et al. states that "[t]o keep the coupling of the marker gene with the foreign protein while

reducing rearrangements and deletions, attempts have been made to introduce sequence elements between the dicistronic reading frames, to which sequence elements ribosomes can bind internally." (see col. 3, lines 35-42). Herlitschka et al. also teaches the use of the SV40 polyadenylation signal in its constructs (see the Examples).

It would have been obvious to one of ordinary skill in the art to modify the construct of Coffin et al. to include a ribosome binding site between the NTR and marker genes. One would have been motivated to do so given the suggestion by Herlitschka et al. that this type of arrangement enables maximum yield of foreign protein, since the gene for the foreign protein is located immediately downstream of the promoter and thus is optimally transcribed. There would have been a reasonable expectation of success given the fact that Herlitschka et al. successfully produced expression cassettes with a ribosome binding site between the foreign gene and the marker gene. It also would have been obvious to include the SV40 polyadenylation signal because it is well known and routine to do so (see Herlitschka et al. Examples). Thus, the invention as a whole was clearly *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

Claims 36, 37, 42 and 62-64 are rejected under 35 U.S.C. 103(a) as being unpatentable over Coffin et al. as applied to claims 1, 2, 4, 7-16, 32-34, 60 and 61 above, and further in view of Anlezark et al. (WO 108288).

The claims are drawn to a composition or kit comprising the herpes simplex virus and an NTR prodrug such as CB1954.

Coffin et al. teaches that the heterologous gene for its HSV constructs preferably encodes a polypeptide of therapeutic use, including polypeptides that are cytotoxic or capable of converting a precursor prodrug into a cytotoxic compound. Polypeptides that are capable of converting a precursor prodrug into a cytotoxic compound include bacterial nitroreductase such as *E. coli* nitroreductase as disclosed in WO 93/108288. Suitable prodrugs include compounds such as those described in WO 93/108288 (see page 3, lines 32-34 and page 9, lines 6-23 of Coffin et al.). WO 93/108288 (Anlezark et al.), which is cited by Coffin et al. and incorporated by reference by Coffin et al., teaches compositions comprising nitroreductase and the prodrug CB1954 (see, for example, page 11, lines 10-21 and page 12, lines 30-35 of Anlezark et al.) for treating cancer.

Therefore, it would have been obvious to one of ordinary skill in the art to combine the constructs of Coffin et al., which encode NTR, with a prodrug such as CB1954 as taught by Anlezark et al. One would have been motivated to do so and there would have been a reasonable expectation of success given the teachings of Anlezark et al.

Thus, the invention as a whole was clearly *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

As for the kit claims, it would have been obvious to one of ordinary skill in the art at the time the invention was made to package components into a kit. One would be motivated to do this for commercial exploitation of the invention by providing convenience for the end user.

Allowable Subject Matter

Claim 3 is objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Nicole E. Kinsey, Ph.D. whose telephone number is (571) 272-9943. The examiner can normally be reached on Monday through Friday from 8:00 am to 5:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Bruce Campell can be reached on (571) 272-0974. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Nicole E. Kinsey, Ph.D.
Examiner
Art Unit 1648

/nk/

/Stacy B. Chen/ 10-29-2007
Primary Examiner, TC1600